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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K | A2

(11) International Publication Number: **WO 99/48461**

(43) International Publication Date: 30 September 1999 (30.09.99)

(21) International Application Number: PCT/US99/06494

(22) International Filing Date: 25 March 1999 (25.03.99)

(30) Priority Data:
60/079,383 26 March 1998 (26.03.98) US

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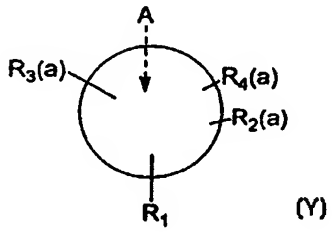
(81) Designated States: AU, CA, GB, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: SUBSTITUTED AROMATIC COMPOUNDS FOR TREATMENT OF ANTIBIOTIC RESISTANT INFECTIONS



(Y)

(57) Abstract

This invention relates to compounds of general formula (Y) wherein A is an aromatic hydrocarbon ring system and R_1 is a carbon bound directly to an oxygen and is also bound to a nitrogen through a saturated carbon and wherein at least one of R_2, R_3 and R_4 is an electron-rich substituent. The active agents are useful for treating patients suffering from infections including gram positive organisms, such as streptococcus, staphylococcus, anthracis, gram negative bacteria such as neisseria species, yeasts and mycobacterium. They are effective against strains which have shown resistance to other antimicrobial agents.

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Title: Substituted Aromatic Compounds for Treatment of Antibiotic Resistant Infections

Field of the Invention:

This invention relates to the treatment of antibiotic-resistant infections, including particularly infections caused by bacteria, mycobacteria, fungi and yeasts. A preferred group of compositions of the invention contain as active agents compounds containing aryl ring systems, including phenyl, naphthyl and anthracene ring systems, substituted by a carbon bound to an oxygen which is also bound to a nitrogen through a saturated carbon or carbon chain which may be substituted with halo, hydroxy, alkoxy, amino or alkylamino are disclosed, In preferred embodiments, the aryl ring system is further substituted by at least two halo substituents or halo-substituted substituents.

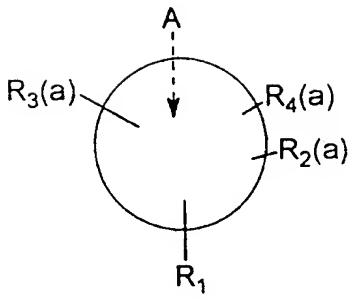
Background of the Invention:

The benefit from use of antibiotics as a means of treating infections has been increasingly compromised by the development of resistant strains of microorganisms. Most of the new drugs are derivatives of older compounds. It is necessary to develop new agents that will respond to the current needs for medicinals that will effectively control pathogenic microbial populations that are resistant to antibiotics.

Halofantrine is a known antimalarial having a phenanthrene ring system substituted by a carbon bound to an oxygen which is also bound to a nitrogen through a saturated CH_2-CH_2 chain to tertiary nitrogen having two butyl substituents. The phenanthrene ring system is further substituted with 2 chlorines and one trifluoromethyl.

Summary of the Invention:

This invention relates to compounds of the general formula:



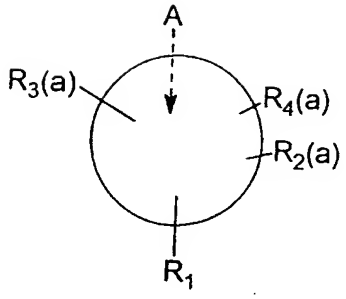
wherein A is a aromatic hydrocarbon ring system and R_1 is a carbon bound directly to an oxygen and is also bound to a nitrogen through a saturated carbon and wherein at least one of R_2, R_3 and R_4 is an electron-rich substituent.

The active agents are useful for treating patients suffering from infections including gram positive organisms, such as streptococcus, staphylococcus, anthracis, gram negative bacteria such as neisseria species, yeasts and mycobacterium. These compounds are effective against strains which have shown resistance to other antimicrobial agents.

Detailed Description of the invention:

This invention relates to compounds that have use in treating several infectious diseases which are now resistant to treatment to conventionally used antibiotics. Some of the compounds described herein have had previously been suggested for use in treating malaria. Some of the compounds are newly discovered. Most of the compounds are lipophilic. The lipid solubility of these compounds should permit the drugs to enter into cells, including cells of the central nervous system. Many of the compounds could be also be absorbed from the intestinal tract when given orally. They may be administered as cyclodextrin inclusion complexes to increase bioavailability. They may also be administered transdermally. Using patches for transdermal administration makes it possible to more easily control dosage.

The active agents for use in accord with the teachings of this disclosure are of the general formula:

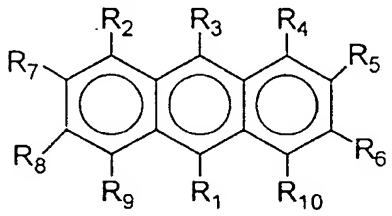


wherein A is an aromatic ring system and R_1 is bound directly to an oxygen and is also bound to a nitrogen through a saturated carbon. R_1 is of the structure CHOZX wherein Z may be hydrogen, a second bond to the oxygen, or may be carboxyl, ether or ester moiety wherein the ether or ester moiety may be alkyl of 1-8 carbons, phenyl, phenylalkyl, wherein the alkyl moiety consists of 1-4 carbons and wherein any said alkyl or phenyl group may, additionally, be substituted with hydroxy, alkyl of 1-2 carbons, alkenyl of 2-3 carbons, halo, amino, or alkyl amino group, X is $(CH_2)_tN((CH2)_n(CH_3))_m$ wherein $_t$ is 1-3, n is ≤ 6, m is 1 or 2 with the proviso that when m is 2, at least one n is <3, or X may be $(CH_2)_oJ$ wherein 0 is 0-4 and J is a saturated nitrogen-containing ring system with up to 10 carbon atoms in the ring system and may have up to 4 bridge carbons, wherein any saturated ring system may be substituted with alkyl, alkenyl, halo, alkoxy or haloalkyl moieties of 1-5 carbons or with phenyl, phenoxy, phenylalkyl, phenylalkoxy, carboxy or carbonyl groups, wherein the carboxy or carbonyl groups, including keto or ester moieties with alkyl groups of 1-4 carbons, alkenyl groups of 2-5 carbons or phenylalkyl wherein the alkyl is of 1-3 carbons or phenylalkoxy wherein the alkyl is of 1-3 carbons. Regarding substituents of $R_2(a)$, $R_3(a)$ and $R_4(a)$, a may be 0-4 with the proviso that at least one a is not 0. R_2, R_3 and R_4 may be alkyl (including cycloalkyl), a saturated, nitrogen-containing ring of 4-10 atoms, alkoxy, aryl, aryloxy, aryloxyalkyl, amino, amino-alkyl, alkyl-aminoalkyl,

arylamino, alkenyl, arylalkenyl, arylalkylaminoalkyl, carboxyalkyl, hydroxy, halo, alkenyl, alkenyloxy, haloalkyl (including perhaloalkyl), wherein any alkyl has 1-8 carbons, alkenyl has 2-8 carbons, wherein halo is chloro, fluoro or bromo and aryl is a ring system of 1-3 rings with the provision that at least one of R_2, R_3 and R_4 is an electron-rich substituent. Z and X may be linked to form a heterocylic ring system. Furthermore, any alkyl or aryl at R_2, R_3 and R_4 may be further substituted with aryl of 1-2 rings, halo, (including multiple halo substitutions) alkyl, haloalkyl or alkoxy. Preferred halo substituents are chloro or bromo and a preferred haloalkyl is trifluoromethyl.

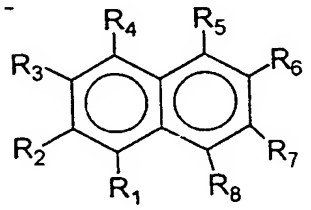
Compounds wherein X is $(CH_2)_oJ$ and o is 2-4 are novel.

Particularly useful compounds are those of Formulas I, II, III and IV.



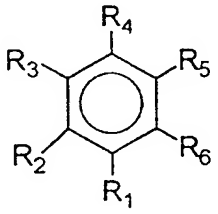
Formula I

In compounds of Formula I, any of R_{2-8} may be substituents designated under R_2, R_3 and R_4 in the general formula above, with the proviso that at least one of R_{2-8} is an electron-rich substituent and any one of R_1, R_9 or R_{10} is a substituent as defined as R_1 in the general formula. Preferred compounds are those having at least two halos groups on the compound, with chloro or trifluoromethyl being particularly preferred groups.



Formula II

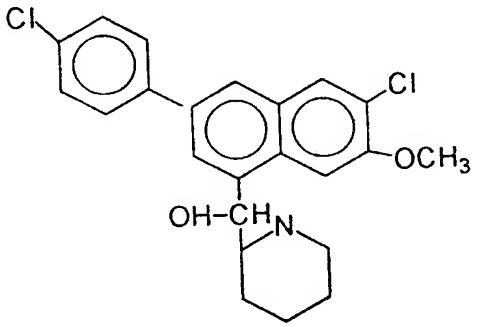
In compounds of Formula II, any of R_{2-8} may be substituents identified as R_2, R_3 or R_4 in the general formula with the proviso that at least one substituents is an electron-rich moiety and R_1 is as designated for R_1 (CHOZX) for the general formula above. Many of the preferred compounds have at least two halo or halo-substituted substituents.



Formula III

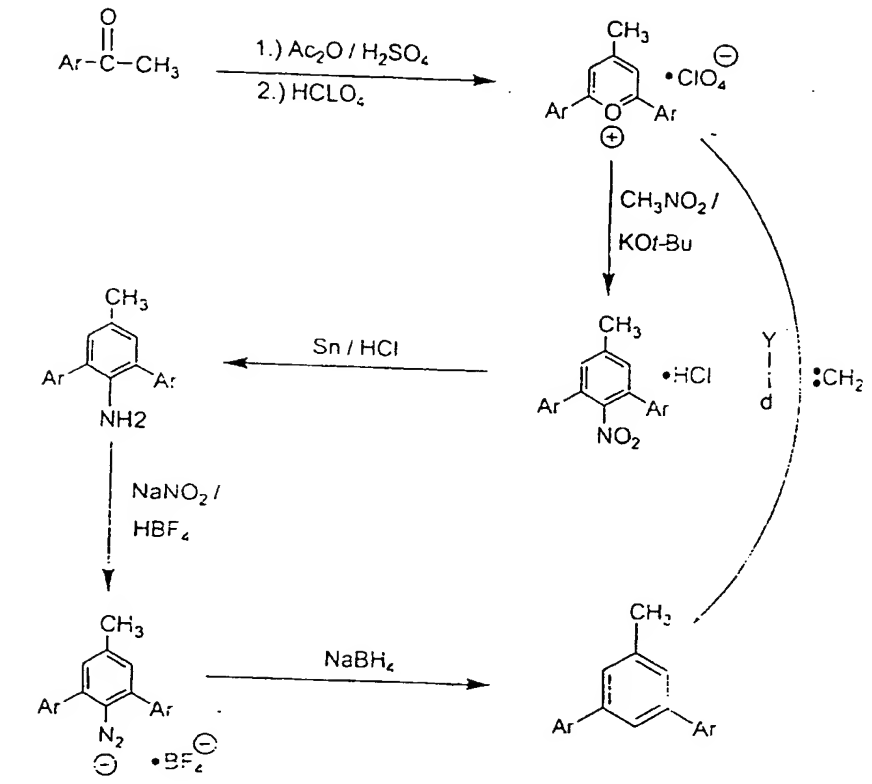
wherein R_1 is defined as in the general formula and R_{2-6} is defined in the same manner as R_2, R_3 and R_4 in the general formula. May of the preferred compounds have least two halo or halo-substituted substituents.

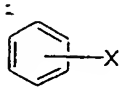
A particularly valuable compound of Formula II is of the formula:



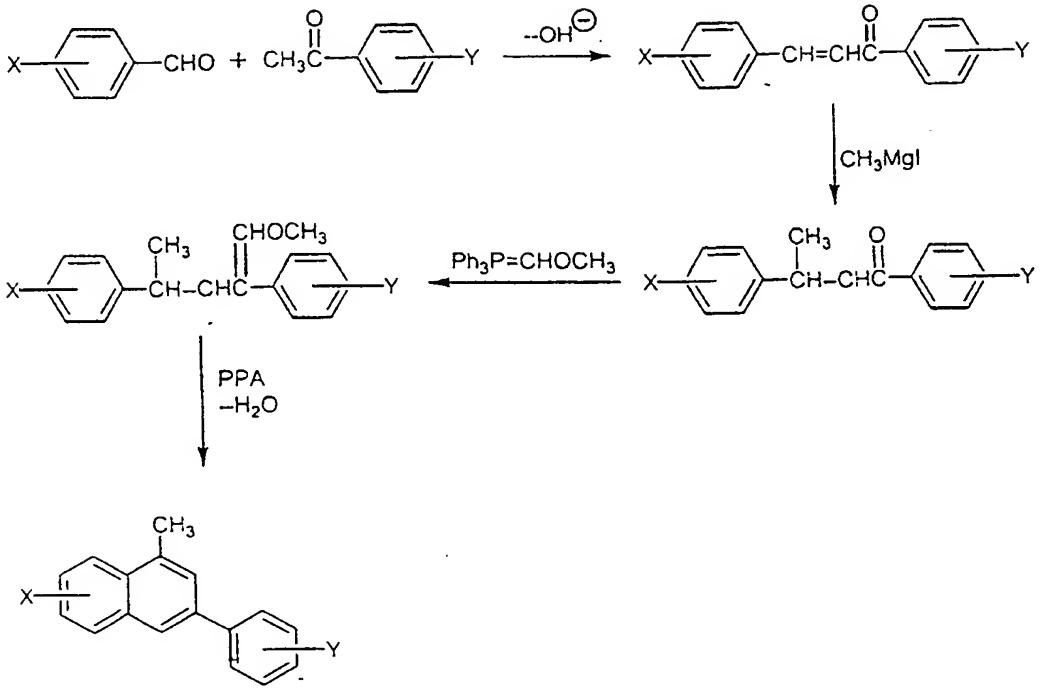
Compounds of Formulas I, II and III can be made using the following methods:

3,5 -Bis(Aryl)phenyltoluene

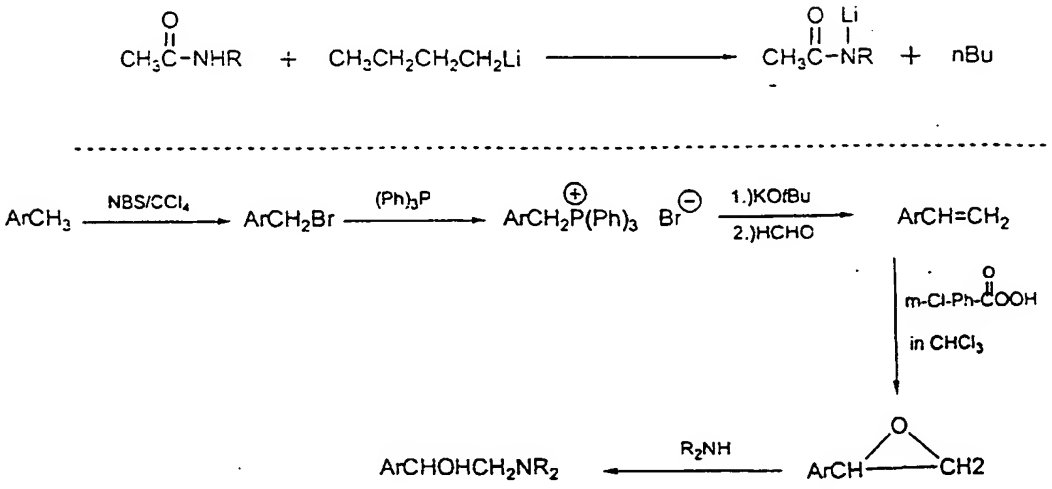


Ar =  Where X is mono- or di- halo, alkoxy, or halogen substituted alkyl. Otherwise X ishydrogen.

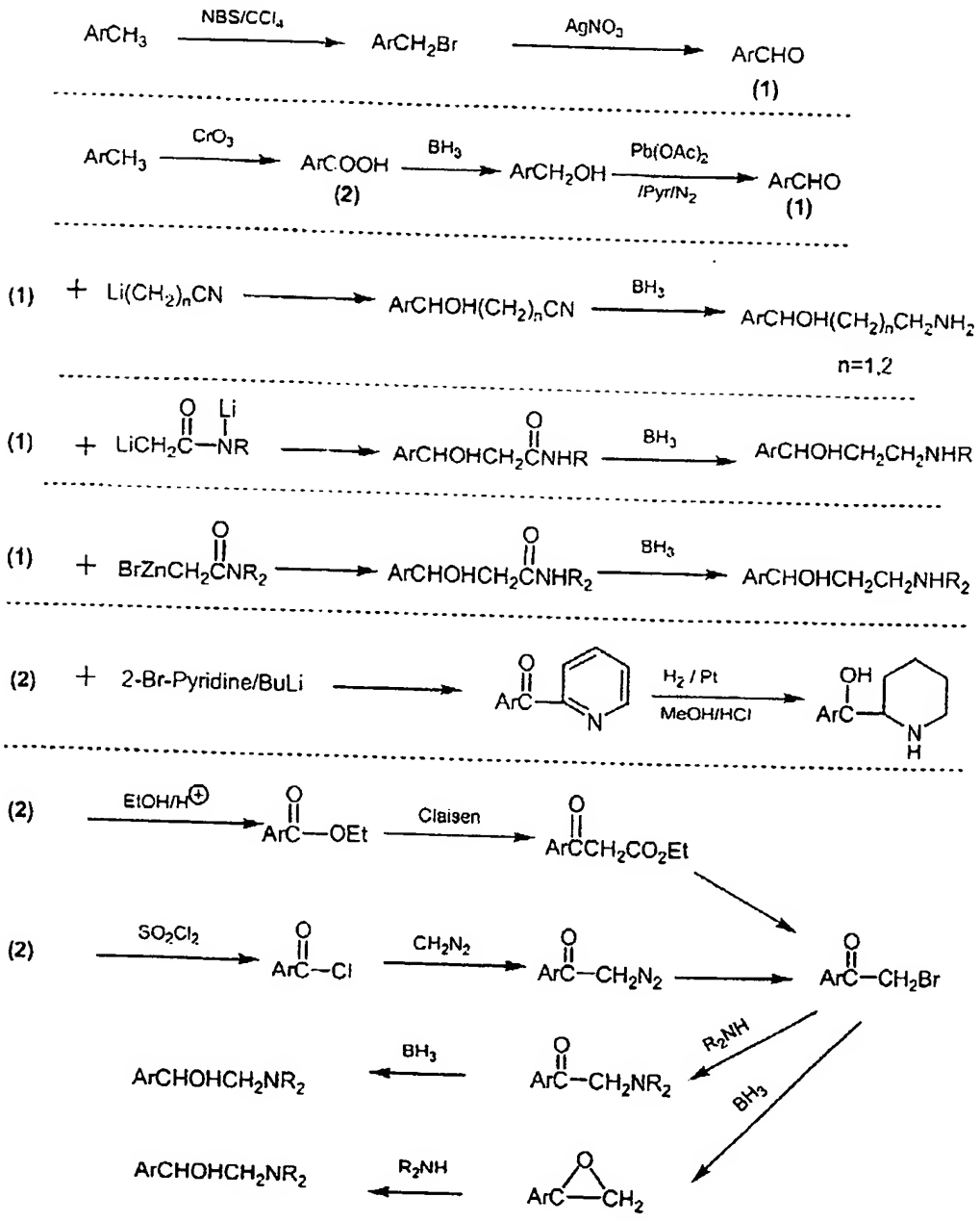
Preparing starting materials:



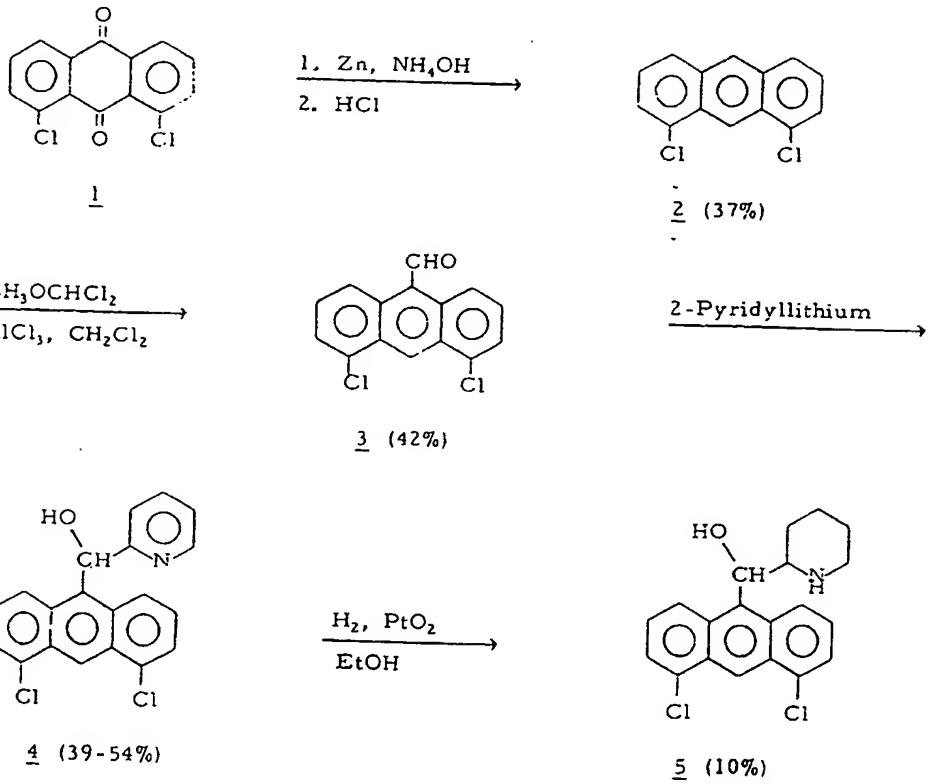
A general method for production:



Side Chain Introductions



α-(2-PIPERIDYL)-4, 5-DICHLORO-9-ANTHRACENEMETHANOL (WR 218394)



1

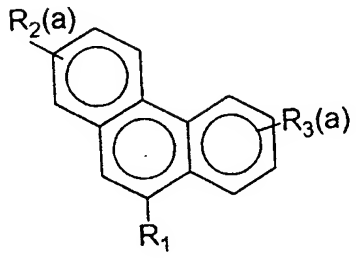
2 (37%)

3 (42%)

4 (39-54%)

5 (10%)

Compounds of the general formula wherein A is a phenanthrene ring are known. Compounds of the following formula:

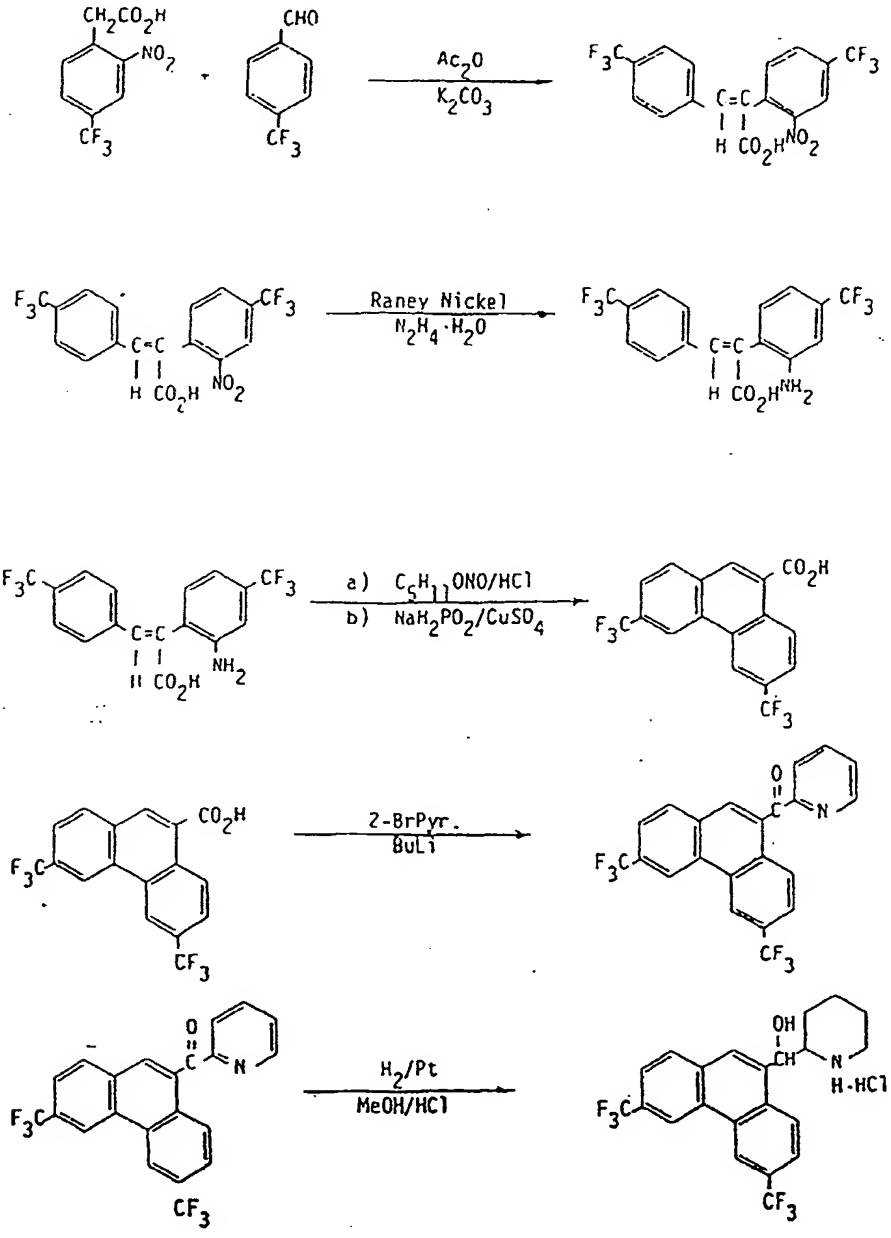


Formula IV

wherein R_1 is a carbon bound directly to an oxygen and is also bound to a nitrogen through a saturated carbon and is of the structure CHOZX wherein Z may be hydrogen, a second bond to the oxygen, or may be carboxyl, ether or ester moiety wherein the ether or ester moiety may be alkyl of 1-8 carbons, phenyl, phenylalkyl, wherein the alkyl moiety consists of 1-4 carbons and wherein any said alkyl or phenyl group may, additionally, be substituted with hydroxy, alkyl of 1-2 carbons, alkenyl of 2-3 carbons, halo, amino, or alkyl amino group, X is $(CH_2)_l N((CH2)_n(CH_3))_m$ wherein $_l$ is 1-3, n is ≤ 6, m is 1 or 2 with the proviso that when m is 2, at least one n is <3, or X may be $(CH_2)_o J$ as defined in the general formula, wherein R_2 and R_3 are as defined in the general formula and a is 0 to 3, with the proviso that for at least one of R_2 or R_3 a is 1 - 3. Preferred halo substituents are chloro or bromo and preferred haloalkyl is trifluoromethyl. A particularly useful member of this group of compounds is desbutylhalofantrin, a compound of the formula:

which has now been found to be superior to halofantrine for treatment of malaria. (See U.S. Patent 5,711,966, which is incorporated herein by reference in its entirety.)

The phenanthrenes may be made by several methods, including the following scheme:



The phenanthrene compounds may also be prepared using the phenanthroic acid chlorides.

Example 1:

To a solution of 2g of 10-(ω-bromoacetyl)-2,7-dichlorophenanthrene in 25 ml of THF is added 2.9 g. of di-n-heptylamine in 5 ml of THF at ambient temperature. After one hour, the THF is evaporated, the residue triturated with pentane, and filtered. The pentane residue is dissolved in EtOH/THF and reacted with 0.42 g of $NaBH_4$ for 1.5 hours. The resulting reaction mixture is concentrated, the diluted with H_2H, extracted with Et_2O, and acidified with gaseous HCl to yield the dichlorophenanthraceneaminoalcohol HCl salt.

Several active agents of the invention were tested for activity against several infectious organisms. Some of the methods used in testing are described below.

Media:

The strains were streaked on blood agar plates (trypticase soy broth containing 5% sheep cells). A single colony was isolated and grown in Mueller-Hinton Broth (MHB) as recommended by the national Committee for Clinical Laboratory Standards for rapidly growing bacteria. Candida species and related yeasts were isolated in a similar manner on brain-heart infusion agar (BHI).

Susceptibility tests:

The antibiotic susceptibility profile of each strain was determined using standard microtiter dilution plates obtained from the Clinical Microbiology Laboratory at Ohio State University Hospitals. The Inocula were prepared by suspending a 4 hour log phase growth in MHB visually equal in turbidity of an 0.5 McFarland standard. Inocula were further diluted and added to microdilution trays to achieve a final density of approximately 1 x 10^5 CFU/ml. The trays were incubated for 16 to 20 hours at 35°C. The highest dilution at which wells remained clear was considered to be the minimum inhibitory concentration (MIC).

The MIC and minimum bacterial concentration (MBC) of the strains to the active agents were determined by two-fold

dilutions in Mueller-Hinton broth. Susceptibility tests for ATCC-obtained microorganisms and clinical isolates of gram positive bacteria including methicillin-susceptible and resistant staphylococci, streptococci, pneumococci and gram negative bacteria, including Enterobacteriaceae, Pseudomonas, Hemophilus and Neisseria, were performed in microtiter plates as described above.

Compounds of the invention were dissolved in 1 ml of methanol and stored in aliquots at -70°C. They were diluted in Mueller-Hinton broth for final screening. Compositions were tested in 0.1 ml volumes by serial dilution in microtiter plates against Staphylococcus aureus methicillin-sensitive ATCC 29213 and the methicillin-resistant wild type T67738, as described above. The T67738 was resistant to most antimicrobial drugs, including ciprofloxacin.

The most active compounds were studied further by time and dose-related killing curve analysis using large inocula (1×10^7 CFU/ml).

The dosage and method of administration will depend on the location of the infection, the condition of the patient and the availability of professional supervision. Methods of administration include parenteral, oral, buccal, nasal or endotracheal routes. The active agents may be administered as sprays. For nasal administration, the active agent may be delivered as a powder that is snorted. Inclusion complexes such as cyclodextrin inclusion complexes would be particularly useful for buccal administration of these active agents.

The compounds of the invention may also be administered topically by any means, including by rectal route. Suppositories, solutions for use as retention enemas, and creams or jellies are appropriate carriers for use in rectal administration. The agents may be administered directly to infected tissue. For example, in case of open wounds, the active agents may be administered in the form of sprays or ointments.

Compounds of the invention may be applied to the skin

or mucosa, including the vaginal mucosa, using creams, jellies, suppositories, or solutions. The active agents of the invention may be delivered directly to the epithelial tissue topically. For example, during surgery compositions containing the active agents of the invention to the applied directly to target tissues and prosthetic devices. The compositions could be given by aerosol into the trachea or administered in mist along with other agents into the respiratory tract.

The compositions of the invention may also be used prophylactically to protect from infection by pathogenic organisms.

Dosage forms containing about 25 to 1000 mg for administration by mouth are suggested for use in adults. However, because the condition and size of the patient and the infectring organisms may differ greatly, eventual dosage requirements must be adjusted by the physician. Hence, dosage suggestions are provided to give general guidance to those of skill in the art. In accord with the purposes of providing such guidance, the following data is provided. The information provided is useful

The concentration required to provide benefit was studied in culture and provides guidance for effective concentration in the blood of the infected animal. The results of these studies may be seen in Tables I and II

TABLE I:

Active agent:		Effective Concentration
R_1 CHOZX	other substitutions:	S. Aureous (Resist).
Formula I		
Z=H, X=CH_2-(2-piperidinyl) (WR 218394)	R_2 and R_4 are Cl	3.1 μg/ml
Formula II		
Z=H, X=CH_2-(2-piperidinyl) (WR 184366) (the acetate)	R_6 = Cl, R_7 = OCH_3, R_3 = 4-Cl-phenyl	3.13 μg/ml
Z=H, X=CH_2-(2-piperidinyl) (WR 185308) (the acetate)	R_6 = Cl, R_7 = OCH_3, R_3 = 3, 4 dichloro-phenyl	6.25 μg/ml

The above compounds are also important for use in treatment of mycobacterial and fungal infections. Other compounds include those of the formula:

Formula I

R_1 is CHOZX and Z=H, $X=CH_2-N(C_4H_9)(C_3H_7)$	R_5 and R_6 are Cl	(WR 201674)
R_1 is CHOZX and Z=H, $X=(CH_2)_2NHC_3H_7$	R_3 is Cl	(WR 198118)
R_1 is CHOZX and Z=H, $X=(CH_2)_2NHC_3H_7$	R_3 is Cl, R_5 is CF_3	(WR 201683)

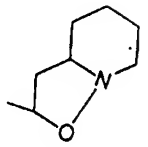
Formula II

Z=H, $X=CH_2$-(2-piperidinyl)	R_6=Cl, $R_7=CF_3$, R_3=4-Cl-phenyl
Z=H, $X=CH_2$-(2-piperidinyl)	$R_6=CF_3$, $R_7=OCH_3$, R_3=3,4 dichloro-phenyl

Formula III

Z=H, $X=CH_2$-(2-piperidinyl)	R_3 and R_5 are 4-Cl-phenyl
Z=H, $X=CH_2$-(2-piperidinyl)	R_3=Cl, $R_5=4-OCH_3$-phenyl
Z=H, $X=CH_2CH_2$(2-piperidinyl)	R_3=Cl, $R_5=4-OCH_3$-phenyl

Formula IV

Active agent:							Effective Concentration		
							S. Aureous		
Z	X	R_2,	n	R_3	n		Sens.	Resist.	Mycobacteria
H	piperidinyl (#1)	CF_3	1	CF_3	1				1.56
H	piperidinyl (#2)	Cl	1	CF_3	1				3.3
H	piperidinyl (#3)	Cl	2	CF_3	1				3.0
H	piperidinyl (#4)	Br	1	Br	1				1.5
H	piperidinyl (#5)	Cl	1	Cl	1				.75
H	CH_2-piperidinyl (#6)	Cl	1	Cl	1				1.56
H	piperidinyl (#7)	CF_3	2	Cl	2				3.0
H	piperidinyl (#8)	CF_3	1	CF_3	1				6.2
H	CH_2-piperidinyl (#9)	Cl	2	CF_3	1				0.8
ZX=	 (#10)	CF_3	1	CF_3	1				6.25
H	$CH_2NHCH(CH_2CH_3)_2$ (#11)	CF_3	1	CF_3	1				3.3
H	$(CH_2)NH(CH_2)_3CH_3$ (#12)	CF_3	1	Cl	2				1.56

Example 2:

Capsules of a formulation of active agent designated #184366 for oral administration are prepared by containing 250 mg. of the active agent, 100 mg. starch, and 5 mg. magnesium stearate. The capsules are administered daily or twice a day to achieve a daily dosage of 500 mg. per day.

Example 3:

A preparation for application to the skin or mucosa may be prepared in the following manner:

Ingredient	%w/w
Compound #185308	15.0%
glyceryl monostearate	3.0%
Petrolatum	83.5%

Example 4:

A formulation for administration as a retention enema may be formulated in the following manner:

Ingredient	w/w %
Compound #218394	15%
Propylene glycol	85%

When the active agent is administered to the mucosa of the oral cavity, it may be administered as a buccal tablet or spray for use in the oral-pharyngeal cavity and the nasal cavities.

Example 5:

To 15 ml of phosphate buffered saline is added 3 mg of compound #185308. The composition is placed in a bottle having a stopper with a smooth glass rod extending into the solution. The composition is applied to boils using the smooth glass rod as an applicator. The composition may also

be administered as a spray from a bottle with an atomizer.

Example 6:

To a 4 X 4 inch bandage having a smooth surface on one side there is applied to the smooth surface .02 ml of the solution prepared as a 2 μM solution of active agent designated # 183308 in PBS. The prepared bandage is then enclosed in a foil covering which is made air-tight. For application, the bandage is unwrapped and is applied smooth side down on the wound.

Example 7:

A composition is prepared for use on the skin or mucosa in the following manner:

Ingredient	%w/w
Agent designated #201683	0.5%
propylene glycol	13.0%
Phosphate buffered saline	86.5%

When the active agent is administered to the mucosa of the oral cavity, it may be administered as a buccal tablet or spray for use in the oral-pharyngeal cavity and the nasal cavities.

Example 8:

A composition prepared as a gel for application to the skin:

Ingredient	%w/w
active agent #1843660	0.5%
propylene glycol	10.0%
Polyethylene glycol	89.5%

Example 9:

A composition prepared for administration as a suppository:

Ingredient	(%w/w)
Active agent #185308	0.5 mg
glyceryl monosterate	1.0 Gm
hydrogenated coconut oil	1.0 Gm
glyceryl monopalmitate	1.0 Gm

Example 10:

A composition for intravenous administration is prepared comprising:

184366	300 mg.
10% glucose in 1/2 normal saline	to 300 ml.

Regarding the compounds of Formula IV (Phenanthrenes), the following examples are provided:

Example 11:

Capsules of a formulation of active agent designated #1 for oral administration are prepared by containing 250 mg. of the active agent, 100 mg. starch, and 5 mg. magnesium stearate. The capsules are administered daily or twice a

day to achieve a daily dosage of 500 mg. per day.

Example 12:

A preparation for application to the skin or mucosa may be prepared in the following manner:

Ingredient	%w/w
Compound #3	15.0%
glyceryl monostearate	3.0%
Petrolatum	83.5%

Example 13:

A formulation for administration as a retention enema may be formulated in the following manner:

Ingredient	w/w %
Compound #10	15%
Propylene glycol	85%

When the active agent is administered to the mucosa of the oral cavity, it may be administered as a buccal tablet or spray for use in the oral-pharyngeal cavity and the nasal cavities.

Example 14:

To 15 ml of phosphate buffered saline is added 3 mg of compound #11. The composition is placed in a bottle having a stopper with a smooth glass rod extending into the solution. The composition is applied to boils using the smooth glass rod as an applicator. The composition may also be administered as a spray from a bottle with an atomizer.

Example 15:

To a 4 X 4 inch bandage having a smooth surface on one

side there is applied to the smooth surface .02 ml of the solution prepared as a 2 μM solution of active agent designated # 4 in PBS. The prepared bandage is then enclosed in a foil covering which is made air-tight. For application, the bandage is unwrapped and is applied smooth side down on the wound.

Example 16:

A composition is prepared for use on the skin or mucosa in the following manner:

Ingredient	%w/w
Agent designated #9	0.5%
propylene glycol	13.0%
Phosphate buffered saline	86.5%

When the active agent is administered to the mucosa of the oral cavity, it may be administered as a buccal tablet or spray for use in the oral-pharyngeal cavity and the nasal cavities.

Example 17:

A composition prepared as a gel for application to the skin:

Ingredient	%w/w
active agent designated #3	0.5%
propylene glycol	10.0%
Polyethylene glycol	89.5%

Example 18:

A composition prepared for administration as a suppository:

Ingredient	(%w/w)
Active agent #8	0.5 mg
glyceryl monosterate	1.0 Gm
hydrogenated coconut oil	1.0 Gm
glyceryl monopalmitate	1.0 Gm

Example 19:

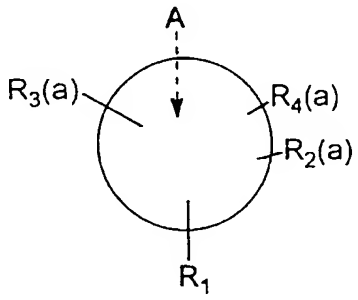
A composition for intravenous administration is prepared comprising:

Desbutylhalofantrine:	300 mg.
10% glucose in 1/2 normal saline	to 300 ml.

The compositions for intravenous administration are particularly valuable for administration intravenously during heart surgery and to patients suffering from endocarditis.

What we claim is:

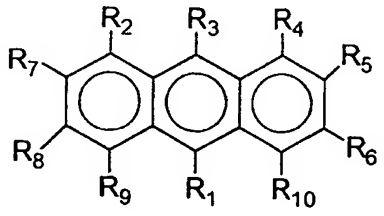
1. A method of treating or preventing infection caused by bacteria, mycobacterium or fungi by administration of a composition containing as an active agent a bacteria, mycobacterium or yeast growth-inhibiting effective amount of a compound of the formula:



wherein A is a hydrocarbon aromatic ring system, R_1 is bound directly to an oxygen and is also bound to a nitrogen through a saturated carbon or carbon chain, with R_1 being of the structure CHOZX wherein Z may be hydrogen, a second bond to the oxygen, or may be carboxyl, ether or ester moiety wherein the ether or ester moiety may be alkyl of 1-8 carbons, phenyl, phenylalkyl, wherein the alkyl moiety consists of 1-4 carbons and wherein any said alkyl or phenyl group may, additionally, be substituted with hydroxy, alkyl of 1-2 carbons, alkenyl of 2-3 carbons, halo, amino, or alkyl amino group and X is $(CH_2)_\iota N((CH2)_n(CH_3))_m$ wherein ι is 1 to 3, n is ≤ 6, m is 1 or 2 with the proviso that when m is 2, at least one of n is <3, or X may be $(CH_2)_oJ$ wherein o is 0-4 and J is a saturated nitrogen-containing ring system with up to 10 carbon atoms in the ring system and may have up to 4 bridge carbons, and wherein any saturated ring system may be substituted with alkyl, alkenyl, halo, alkoxy or haloalkyl moieties of 1-5 carbons or with phenyl, phenoxy, phenylalkyl, phenylalkoxy, carboxy or carbonyl groups, wherein the carboxy or carbonyl groups, including keto or ester

moieties, with alkyl groups having 1-4 carbons, alkenyl groups of 2-5 carbons or phenylalkyl wherein the alkyl is of 1-3 carbons or phenylalkoxy wherein the alkyl is of 1-3 carbons and, further, wherein X and Z may be linked to form a heterocyclic ring system and (a) is 0-4 with the proviso that at least one of (a) is not 1, R_2, R_3 and R_4 may be alkyl (including cycloalkyl), a saturated, nitrogen-containing ring of 4-10 atoms, alkoxy, aryl, aryloxy, aryloxyalkyl, amino, amino-alkyl, alkyl-aminoalkyl, arylamino, alkenyl, arylalkenyl, arylalkylaminoalkyl, carboxyalkyl, hydroxy, halo, alkenyl, or alkenyloxy, halo-substituted alkyl, wherein any alkyl has 1-8 carbons, alkenyl has 2-8 carbons, wherein halo is chloro, fluoro or bromo and aryl is a ring system of 1-3 rings and wherein any alkyl or aryl at R_2, R_3 and R_4 may be further substituted with halo (including multiple halo subtitutions), aryl of 1-2 rings, alkyl, haloalkyl or alkoxy, with the proviso that at least one of R_2, R_3 and R_4 is an electron-rich substituent.

2. A method of claim 1 of treating or preventing infection caused by bacteria, mycobacterium or fungi by administration of a composition containing as an active agent a bacteria, mycobacterium or yeast growth-inhibiting effective amount of a compound of the formula:



Formula I

wherein any of R_2, R_3, R_4, R_5, R_6, R_7 and R_8 may be H, alkyl (including cycloalkyl), a saturated, nitrogen-containing ring of 4-10 atoms, alkoxy, aryl, aryloxy, aryloxyalkyl, amino, amino-alkyl, alkyl-aminoalkyl, arylamino, alkenyl, arylalkenyl, arylalkylaminoalkyl,

carboxyalkyl, hydroxy, halo, alkenyl, or alkenyloxy, halo-substituted alkyl, wherein any alkyl has 1-8 carbons, alkenyl has 2-8 carbons, wherein halo is chloro, fluoro or bromo and aryl is a ring system of 1-3 rings and wherein any alkyl or aryl may be further substituted with halo (including multiple halo subtitutions), aryl of 1-2 rings, alkyl, haloalkyl or alkoxy, with the proviso that at least one of R_2, R_3, R_4, R_5, R_6, R_7 and R_8 is an electron-rich substituent and one of R_1, R_9 or R_{10} is bound directly to an oxygen and is also bound to a nitrogen through a saturated carbon or carbon chain, being of the structure CHOZX wherein Z may be hydrogen, a second bond to the oxygen, or may be carboxyl, ether or ester moiety wherein the ether or ester moiety may be alkyl of 1-8 carbons, phenyl, phenylalkyl, wherein the alkyl moiety consists of 1-4 carbons and wherein any said alkyl or phenyl group may, additionally, be substituted with hydroxy, alkyl of 1-2 carbons, alkenyl of 2-3 carbons, halo, amino, or alkyl amino group and X is $(CH_2)_l N((CH2)_n(CH_3))_m$ wherein $_l$ is 1-3, n is ≤ 6, m is 1 or 2 with the proviso that when m is 2, at least one n is <3, or X may be $(CH_2)_o J$ wherein o is 0-4 and J is a saturated nitrogen-containing ring system with up to 10 carbon atoms in the ring system and may have up to 4 bridge carbons, and wherein any saturated ring system may be substituted with alkyl, alkenyl, halo, alkoxy or haloalkyl moieties of 1-5 carbons or with phenyl, phenoxy, phenylalkyl, phenylalkoxy, carboxy or carbonyl groups, wherein the carboxy or carbonyl groups, including keto or ester moieties, with alkyl groups having 1-4 carbons, alkenyl groups of 2-5 carbons or phenylalkyl wherein the alkyl is of 1-3 carbons or phenylalkoxy wherein the alkyl is of 1-3 carbons and, furthermore, X and Z may be linked to form a heterocyclic ring system.

3. A method of claim 2 wherein at least two of R_2, R_3, R_4,

R_5, R_6, R_7 and R_8 are Cl or F_3C.

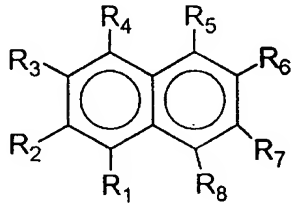
4. A method of claim 2 wherein Z=H, X=CH_2-(2-piperidine) R_2 and R_4 are Cl.

5. A method of claim 2 wherein R_9 is CHOZX and Z=H, X=CH_2-$N(C_4H_9)(C_3H_7)$ and R_5 and R_6 are Cl.

6. A method of claim 2 wherein R_1 is CHOZX and Z=H, X=$(CH_2)_2NH(C_3H_7)$ and R_3 is Cl.

7. A nethod of claim 2 wherein R_1 is CHOZX and Z=H, X=$(CH_2)_2NH(C_3H_7)$, R_3 is Cl and R_5 is CF_3.

8. A method of of claim 1 of treating or preventing infection caused by bacteria, mycobacterium or fungi by administration of a composition containing as an active agent a bacteria, mycobacterium or yeast growth-inhibiting effective amount of a compound of the formula:



Formula II

wherein any of R_2, R_3, R_4, R_5, R_6, R_7 and R_8 may be H, alkyl (including cycloalkyl), a saturated, nitrogen-containing ring of 4-10 atoms, alkoxy, aryl, aryloxy, aryloxyalkyl, amino, amino-alkyl, alkyl-aminoalkyl, arylamino, alkenyl, arylalkenyl, arylalkylaminoalkyl, carboxyalkyl, hydroxy, halo, alkenyl, or alkenyloxy, halo-substituted alkyl, wherein any alkyl has 1-8 carbons, alkenyl has 2-8 carbons, wherein halo is chloro, fluoro or bromo and aryl is a ring system of 1-3 rings and wherein any alkyl or aryl may be further substi-

tuted with halo (including multiple halo subtitutions), aryl of 1-2 rings, alkyl, haloalkyl or alkoxy, with the proviso that at least one of R_2, R_3, R_4, R_5, R_6, R_7 and R_8 is an electron-rich substituent and one of R_1, is bound directly to an oxygen and is also bound to a nitrogen through a saturated carbon or carbon chain, being of the structure CHOZX wherein Z may be hydrogen, a second bond to the oxygen, or may be carboxyl, ether or ester moiety wherein the ether or ester moiety may be alkyl of 1-8 carbons, phenyl, phenylalkyl, wherein the alkyl moiety consists of 1-4 carbons and wherein any said alkyl or phenyl group may, additionally, be substituted with hydroxy, alkyl of 1-2 carbons, alkenyl of 2-3 carbons, halo, amino, or alkyl amino group and X is $(CH_2)_l N((CH2)_n(CH_3))_m$ wherein $_l$ is 1-3, n is ≤ 6, m is 1 or 2 with the proviso that when m is 2, at least one n is <3, or X may be $(CH_2)_o J$ wherein o is 0-4 and J is a saturated nitrogen-containing ring system with up to 10 carbon atoms in the ring system and may have up to 4 bridge carbons, and wherein any saturated ring system may be substituted with alkyl, alkenyl, halo, alkoxy or haloalkyl moieties of 1-5 carbons or with phenyl, phenoxy, phenylalkyl, phenylalkoxy, carboxy or carbonyl groups, wherein the carboxy or carbonyl groups, including keto or ester moieties, with alkyl groups having 1-4 carbons, alkenyl groups of 2-5 carbons or phenylalkyl wherein the alkyl is of 1-3 carbons or phenylalkoxy wherein the alkyl is of 1-3 carbons and, furthermore, X and Z may be linked to form a heterocyclic ring system.

9. A method of claim 8 wherein Z=H, X=CH_2-(2-piperidine) R_6 = Cl, R_7 = OCH_3, R_3 = 4-Cl-phenyl.

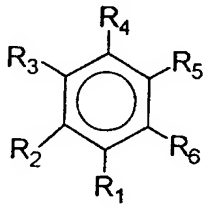
10. A method of claim 8 wherein Z=H, X=CH_2-(2-piperidine) R_6 = Cl, R_7 = OCH_3, R_3 = 3,4 dichloro-phenyl.

11. A method of claim 8 wherein Z=H, X=CH_2-(2-piperidine)

R_6=Cl, R_7=CF_3, R_3=4-Cl-phenyl.

12. A method of claim 8 wherein Z=H, X=CH_2-(2-piperidine) R_6=CF_3, R_7=OCH_3, R_3=3,4-diclhoro-phenyl.

13. A method of claim 1 of treating or preventing infection caused by bacteria, mycobacterium or fungi by administration of a composition containing as an active agent a bacteria, mycobacterium or yeast growth-inhibiting effective amount of a compound of the formula:



Formula III

wherein any of R_2, R_3, R_4, R_5, and R_6, may be H, alkyl (including cycloalkyl), a saturated, nitrogen-containing ring of 4-10 atoms, alkoxy, aryl, aryloxy, aryloxyalkyl, amino, amino-alkyl, alkyl-aminoalkyl, arylamino, alkenyl, arylalkenyl, arylalkylaminoalkyl, carboxyalkyl, hydroxy, halo, alkenyl, or alkenyloxy, halo-substituted alkyl, wherein any alkyl has 1-8 carbons, alkenyl has 2-8 carbons, wherein halo is chloro, fluoro or bromo and aryl is a ring system of 1-3 rings and wherein any alkyl or aryl may be further substituted with halo (including multiple halo subtitutions), aryl of 1-2 rings, alkyl, haloalkyl or alkoxy, with the proviso that at least one of R_2, R_3, R_4, R_5, R_6, R_7 and R_8 is an electron-rich substituent and one of R_1, is bound directly to an oxygen and is also bound to a nitrogen through a saturated carbon or carbon chain, being of the structure CHOZX wherein Z may be hydrogen, a second bond to the oxygen, or may be carboxyl, ether or ester moiety wherein the ether or ester moiety may be alkyl of 1-8 carbons, phenyl, phenylalkyl, wherein the alkyl moiety consists of 1-4 carbons and wherein any said alkyl or phenyl group may, additionally, be substituted

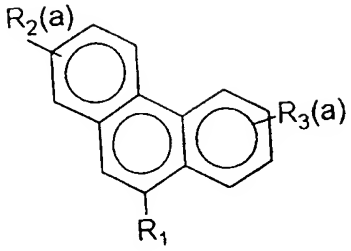
with hydroxy, alkyl of 1-2 carbons, alkenyl of 2-3 carbons, halo, amino, or alkyl amino group and X is $(CH_2)_t N((CH2)_n(CH_3))_m$ wherein $_t$ is 1-3, n is ≤ 6, m is 1 or 2 with the proviso that when m is 2, at least one n is <3, or X may be $(CH_2)_o J$ wherein o is 0-4 and J is a saturated nitrogen-containing ring system with up to 10 carbon atoms in the ring system and may have up to 4 bridge carbons, and wherein any saturated ring system may be substituted with alkyl, alkenyl, halo, alkoxy or haloalkyl moieties of 1-5 carbons or with phenyl, phenoxy, phenylalkyl, phenylalkoxy, carboxy or carbonyl groups, wherein the carboxy or carbonyl groups, including keto or ester moieties, with alkyl groups having 1-4 carbons, alkenyl groups of 2-5 carbons or phenylalkyl wherein the alkyl is of 1-3 carbons or phenylalkoxy wherein the alkyl is of 1-3 carbons, and, furthermore, X and Z may be linked to form a heterocyclic ring system.

14. A method of claim 13 wherein Z=H, $X=CH_2$-(2-piperidine) R_3 and R_5 are 4-Cl-phenyl.

15. A method of claim 13 wherein Z=H, $X=CH_2$-(2-piperidine) R_3=Cl, R_5=4-OCH_3-phenyl.

16. A method of claim 13 wherein Z=H, $X=CH_2CH_2$(2-piperidine) R_3=Cl, R_5=4-OCH_3-phenyl

17. A method of of claim 1 of treating or preventing infection caused by bacteria, mycobacterium or fungi by administration of a composition containing as an active agent a bacteria, mycobacterium or yeast growth-inhibiting effective amount of a compound of the formula:



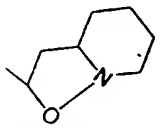
Formula IV

wherein any (a) is 1-3 and R_2, and R_3, may be H, alkyl (including cycloalkyl), a saturated, nitrogen-containing ring of 4-10 atoms, alkoxy, aryl, aryloxy, aryloxy-alkyl, amino, amino-alkyl, alkyl-aminoalkyl, arylamino, alkenyl, arylalkenyl, arylalkylaminoalkyl, carboxy-alkyl, hydroxy, halo, alkenyl, or alkenyloxy, halo-substituted alkyl, wherein any alkyl has 1-8 carbons, alkenyl has 2-8 carbons, wherein halo is chloro, fluoro or bromo and aryl is a ring system of 1-3 rings and wherein any alkyl or aryl may be further substituted with halo (including multiple halo subtitutions), aryl of 1-2 rings, alkyl, haloalkyl or alkoxy, with the proviso that at least one of R_2, R_3, R_4, R_5, R_6, R_7 and R_8 is an electron-rich substituent and one of R_1, is bound directly to an oxygen and is also bound to a nitrogen through a saturated carbon or carbon chain, being of the structure CHOZX wherein Z may be hydrogen, a second bond to the oxygen, or may be carboxyl, ether or ester moiety wherein the ether or ester moiety may be alkyl of 1-8 carbons, phenyl, phenylalkyl, wherein the alkyl moiety consists of 1-4 carbons and wherein any said alkyl or phenyl group may, additionally, be substituted with hydroxy, alkyl of 1-2 carbons, alkenyl of 2-3 carbons, halo, amino, or alkyl amino group and X is $(CH_2)_t N((CH2)_n(CH_3))_m$ wherein $_t$ is 1-3, n is ≤ 6, m is 1 or 2 with the proviso that when m is 2, at least one n is <3, or X may be $(CH_2)_o J$ wherein o is 0-4 and J is a saturated nitrogen-containing ring system with up to 10

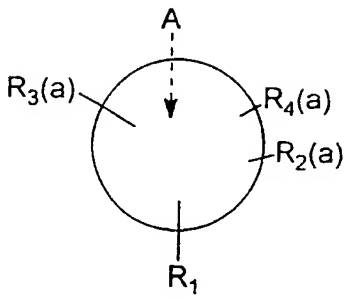
carbon atoms in the ring system and may have up to 4 bridge carbons, and wherein any saturated ring system may be substituted with alkyl, alkenyl, halo, alkoxy or haloalkyl moieties of 1-5 carbons or with phenyl, phenoxy, phenylalkyl, phenylalkoxy, carboxy or carbonyl groups, wherein the carboxy or carbonyl groups, including keto or ester moieties, with alkyl groups having 1-4 carbons, alkenyl groups of 2-5 carbons or phenylalkyl wherein the alkyl is of 1-3 carbons or phenylalkoxy wherein the alkyl is of 1-3 carbons, and, furthermore, X and Z may be linked to form a heterocyclic ring system.

18. A method of claim 17 wherein the active agent is desbutyl-halofantrine.

19. A method of claim 17 wherein the active agent is chosen from among compounds wherein

Z	X	R_2,	n	R_3	n
H	piperidinyl (#1)	CF_3	1	CF_3	1
H	piperidinyl (#2)	Cl	1	CF_3	1
H	piperidinyl (#3)	Cl	2	CF_3	1
H	piperidinyl (#4)	Br	1	Br	1
H	piperidinyl (#5)	Cl	1	Cl	1
H	CH_2-piperidinyl (#6)	Cl	1	Cl	1
H	piperidinyl (#7)	CF_3	2	Cl	2
H	piperidinyl (#8)	CF_3	1	CF_3	1
H	CH_2-piperidinyl(#9)	Cl	2	CF_3	1
ZX=	 (#10)	CF_3	1	CF_3	1
H	$CH_2NHCH(CH_2CH_3)_2$ (#11)	CF_3	1	CF_3	1
H	$(CH_2)NH(CH_2)_3CH_3$ (#12)	CF_3	1	Cl	2

20. A compound of the formula:



wherein A is a hydrocarbon aromatic ring system, R_1 is bound directly to an oxygen and is also bound to a nitrogen through a saturated carbon or carbon chain, with R_1 being of the structure CHOZX wherein Z may be hydrogen, a second bond to the oxygen, or may be carboxyl, ether or ester moiety wherein the ether or ester moiety may be alkyl of 1-8 carbons, phenyl, phenylalkyl, wherein the alkyl moiety consists of 1-4 carbons and wherein any said alkyl or phenyl group may, additionally, be substituted with hydroxy, alkyl of 1-2 carbons, alkenyl of 2-3 carbons, halo, amino, or alkyl amino group and X $(CH_2)_oJ$ wherein o is 2-4 and J is a saturated nitrogen-containing ring system with up to 10 carbon atoms in the ring system and may have up to 4 bridge carbons, and wherein any saturated ring system may be substituted with alkyl, alkenyl, halo, alkoxy or haloalkyl moieties of 1-5 carbons or with phenyl, phenoxy, phenylalkyl, phenylalkoxy, carboxy or carbonyl groups, wherein the carboxy or carbonyl groups, including keto or ester moieties, with alkyl groups having 1-4 carbons, alkenyl groups of 2-5 carbons or phenylalkyl wherein the alkyl is of 1-3 carbons or phenylalkoxy wherein the alkyl is of 1-3 carbons, and (a) is 0-4 with the proviso that at least one of (a) is not 1, R_2, R_3 and R_4 may be alkyl (including cycloalkyl), a saturated, nitrogen-containing ring of 4-10 atoms, alkoxy,

aryl, aryloxy, aryloxyalkyl, amino, amino-alkyl, alkyl-aminoalkyl, arylamino, alkenyl, arylalkenyl, arylalkyl-aminoalkyl, carboxyalkyl, hydroxy, halo, alkenyl, or alkenyloxy, halo-substituted alkyl, wherein any alkyl has 1-8 carbons, alkenyl has 2-8 carbons, wherein halo is chloro, fluoro or bromo and aryl is a ring system of 1-3 rings and wherein any alkyl or aryl at R_2, R_3 and R_4 may be further substituted with halo (including multiple halo subtitutions), aryl of 1-2 rings, alkyl, haloalkyl or alkoxy, with the proviso that at least one of R_2, R_3 and R_4 is an electron-rich substituent.

21. A compound of claim 20 wherein A is a benzene ring.

22. A compound of claim 20 wherein A is a phenanthrene ring.

23. A compound of claim 20 wherein A is naphthalene ring.

24. A compound of claim 20 wherein A is anthracene ring.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/35 | A3

(11) International Publication Number: **WO 99/48461**

(43) International Publication Date: 30 September 1999 (30.09.99)

(21) International Application Number: PCT/US99/06494

(22) International Filing Date: 25 March 1999 (25.03.99)

(30) Priority Data:
60/079,383 26 March 1998 (26.03.98) US

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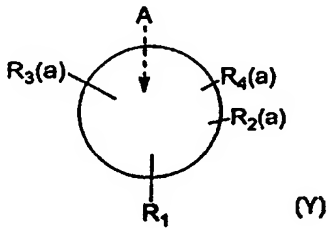
(81) Designated States: AU, CA, GB, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
16 December 1999 (16.12.99)

(54) Title: SUBSTITUTED AROMATIC COMPOUNDS FOR TREATMENT OF ANTIBIOTIC RESISTANT INFECTIONS



(Y)

(57) Abstract

This invention relates to compounds of general formula (Y) wherein A is an aromatic hydrocarbon ring system and R_1 is a carbon bound directly to an oxygen and is also bound to a nitrogen through a saturated carbon and wherein at least one of R_2, R_3 and R_4 is an electron-rich substituent. The active agents are useful for treating patients suffering from infections including gram positive organisms, such as streptococcus, staphylococcus, anthracis, gram negative bacteria such as neisseria species, yeasts and mycobacterium. They are effective against strains which have shown resistance to other antimicrobial agents.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/06494

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/35
US CL :514/454

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/454

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS-on-line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,461,078 A (PATTERSON) 24 October 1995, see the entire document.	1, 2-7, 20 and 24

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 29 SEPTEMBER 1999	Date of mailing of the international search report 01 November 1999 (01.11.99)
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer KEVIN E. WEDDINGTON Telephone No. (703) 308-1235 JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/06494

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2-7, 20 and 24

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/06494

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I, claim(s)1, 2-7, 20 and 24 are drawn to a method of treating or preventing infection caused by bacteria, mycobacterium or fungi with a compound with an anthracene ring system.

Group II, claim(s) 1, 8-12, 20 and 23 are drawn to a method of treating and preventing infection caused by bacteria, mycobacterium or fungi with a compound with a naphthalene ring system.

Group III, claim(s) 1, 13-16, 20 and 21 are drawn to a method of treating or preventing infection caused by bacteria, mycobacterium or fungi with a compound with a benzene ring system.

Group IV, claim(s) 1, 17-20 and 22 are drawn to a method of treating or preventing infection caused by bacteria, mycobacterium or fungi with a compound with a phenanthrene ring system.

The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
The four inventions are independent and distinct, each from the other as they have acquired a separate status in the art as shown by their separate subject matter using different ring systems (species) to treat or prevent infections.